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Exploiting Novel Process Windows for the Synthesis of *meso*-Substituted Porphyrins under Continuous Flow Conditions

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

www.rsc.org/

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Porphyrin synthesis by classical methods frequently involves the use of high temperatures, toxic and dangerous reagents yielding the product in very low amounts and with poor scalability. Herein, we have studied the synthesis of *meso*-substituted porphyrins under continuous flow conditions, thus demonstrating scale-up for the porphyrin synthesis in a safe, cost-competitive, highly pure, reproducible and robust manner.

Introduction

Porphyrins are natural and synthetic compounds whose physical and chemical properties make them the subject of study for many researchers. They have been applied in medicine,[1] catalysis,[2] dye-sensitised solar cells,[3] sensors,[4] molecular electronics and non-linear optics.[5]

Numerous publications on porphyrins have justified the importance of methodological studies, since the development and improvement of synthetic strategies should enable a wide variety and availability of porphyrins and their derivatives. In general, the synthesis of porphyrins involves approaches through mono-pyrrole tetramerisation, or more complex procedures by coupling two dipyrromethanes, or tripyrrane and diformylpyrroles.[6]

The synthesis of *meso*-substituted porphyrins was first reported by Rothemund in 1935, in which pyrrole and benzaldehyde were heated in pyridine in a sealed tube giving *meso*-tetraphenylporphyrin (TPP) in 10% yield.[7] Subsequently, Adler and co-workers reacted equimolar quantities of pyrrole and benzaldehyde at reflux with air oxidation, thus obtaining TPP in yields up to 20%.[8] Lindsey and co-workers developed a two-step reaction, in which the porphyrinogen intermediate was formed by reacting benzaldehyde and pyrrole in dichloromethane under $BF_3.OEt_2$ catalysis, followed by oxidation with 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ), giving TPP in 40% yield. This procedure appears to be one of the best considering the yield, however, it is not easily scalable because of the required high dilution (0.01 M).[9] Also, a mixture of acetic or propionic acid and nitrobenzene as solvent/oxidant was described to synthesize TPP by Gonsalves and co-workers in a one-pot procedure to obtain about 20% yield.[10]

Since then, several new or adapted methodologies have been published that include the use of a micellar environment,[11] ionic liquids,[12] Lewis acid catalysis,[13] clay catalysis,[14] mixed solvents,[15] transition metal ions,[16] and microwave assisted synthesis.[17] Despite numerous publications on porphyrin synthesis, most of them are difficult, laborious and often result in low yields, especially when trying to scale-up the synthesis. In addition, almost all these procedures involve highly toxic reagents and solvents, with low security during their manipulations in gram-scale quantities.

Recently, enabling technologies have revolutionised many fields of chemical synthesis with special highlight for the continuous flow process. This technology has been employed both in the pharmaceutical industry and in research laboratories due to advantages as micromixing, rapid heat transfer, exact control of residence time, automated reaction optimization, multi-step reactions in a continuous sequence, the use of immobilized catalysts, safe manipulation of hazardous reagents, easy scale-up, automated purification, and integrated analytics and screening.[18] Several single-step and multi-step reactions under continuous flow conditions have been reported for the synthesis of active pharmaceutical ingredients (APIs),[19] sugars,[20] peptides,[21] Suzuki–Miyaura coupling reagents,[22] natural products,[23] biocatalyzed reactions,[24] and also for various other transformations.[25]

Herein, we have explored the one-pot synthesis of *meso*-tetraarylporphyrins and *meso*-tetraalkylporphyrins under continuous flow conditions, and demonstrated the synthesis of *meso*-tetraphenylporphyrin on a multi-gram scale. Our continuous flow protocol proves to be safe due to the automation, and also cost-competitive, reproducible and robust, thus yielding several different *meso*-substituted porphyrins.

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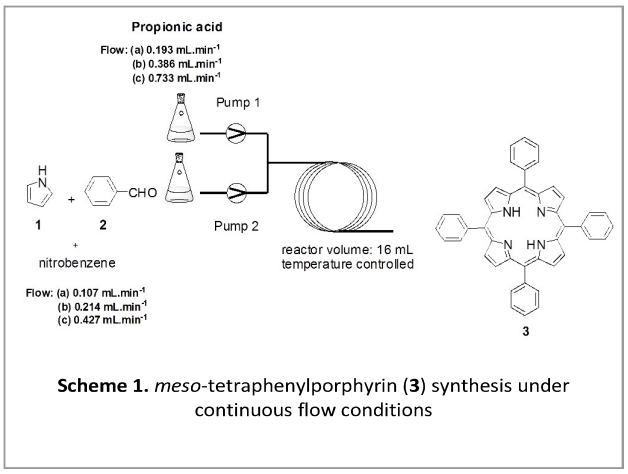
† Electronic Supplementary Information (ESI) available: copy of UV-Vis, ^1H and ^{13}C NMR spectra, LC/MS data of all compounds. See DOI: 10.1039/x0xx00000x

Results and discussion

The porphyrin synthesis under continuous flow was performed using a heated stainless steel tubular reactor and a double channel syringe pump (Scheme 1). Reagents were pumped from different channels (Pump 1: propionic acid; Pump 2: pyrrole + benzaldehyde + nitrobenzene) to a mixing zone and then to the high temperature tubular reactor in order to prevent the early polymerization of reactants. Also, we established a 2:1 flow ratio between Pump 1 and Pump 2 in order to keep an adequate dilution of these reactants. The molar ratio between pyrrole (**1**) and the different tested aldehydes was 1:1 and expressed in mol.L^{-1} (M) for each reactant. All the reactions were performed starting with 12 mmol of each reactant. The porphyrins were isolated by simple precipitation from methanol and further crystallization from CH_2Cl_2 (a few drops) and methanol, unless when further purification is specified.

The reaction conditions were optimized varying reagent concentrations, temperature and flow rates for the synthesis of *meso*-tetraphenylporphyrin (**3**) (Scheme 1) and the results are detailed in Tables 1-3. For each reagent concentration we evaluated the influence of the temperature at three different flow rates.



Scheme 1. *meso*-tetraphenylporphyrin (**3**) synthesis under continuous flow conditions

Starting from the concentrations of 0.1 M for both pyrrole (**1**) and benzaldehyde (**2**), using a flow rate of 1.2 mL.min^{-1} and varying the temperature from 100°C to 160°C, the yields of TPP (**3**) ranged from 1 to 7% (entries 1-4, Table 1). Keeping the same reagent concentrations (0.1 M) and the same temperature range, but using a flow rate of 0.6 mL.min^{-1}, the yields ranged from 2 to 10% (entries 5-8, Table 1), and with a flow rate of 0.3 mL.min^{-1} the yields ranged from 8 to 25% (entries 9-12, Table 1), leading to a space-time yield (STY) of 1.65 g.day^{-1} at the best reaction conditions (entry 10, Table 1). Furthermore, at 0.2 M the best conditions were achieved by using a flow rate of 0.6 mL.min^{-1} at 140°C, thus resulting in a residence time of 27 min, 31% yield, and a space-time yield of 8.17 g.day^{-1} of TPP (**3**) (entry 7, Table 2). Using a higher reagent concentration (0.3 M), 0.3 mL.min^{-1} and 120°C, **3** was synthesized in 27% yield and space-time yield of 5.46 g.day^{-1} (entry 10, Table 3).

Table 1. Optimization of TPP (**3**) synthesis using reagent concentrations at 0.1 M.

Entry	Flow rate (mL.min-1)	T (°C)	Residence time (min)	TPP (**3**) Yield (%)	STY (**3**) (g/day)
1	1.2	100	13	1	0.3
2	1.2	120	13	4	1.0
3	1.2	140	13	7	1.9
4	1.2	160	13	1	0.2
5	0.6	100	27	2	0.3
6	0.6	120	27	10	1.3
7	0.6	140	27	9	1.3
8	0.6	160	27	2	0.3
9	0.3	100	53	8	0.6
10	0.3	120	53	25	1.6
11	0.3	140	53	11	0.8
12	0.3	160	53	5	0.3

Table 2. Optimization of TPP (**3**) synthesis using reagent concentrations at 0.2 M.

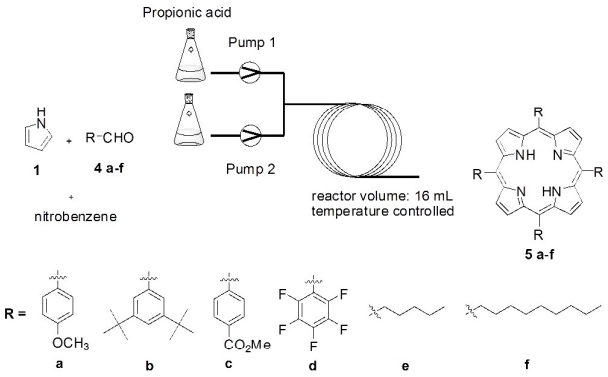
Entry	Flow rate (mL.min-1)	T (°C)	Residence time (min)	TPP (**3**) Yield (%)	STY (**3**) (g/day)
1	1.2	100	13	traces	-
2	1.2	120	13	3	1.7
3	1.2	140	13	13	6.9
4	1.2	160	13	2	1.3
5	0.6	100	27	traces	-
6	0.6	120	27	16	4.4
7	0.6	140	27	31	8.2
8	0.6	160	27	4	1.0
9	0.3	100	53	7	1.0
10	0.3	120	53	29	3.8
11	0.3	140	53	10	1.4
12	0.3	160	53	5	0.6

Table 3. Optimization of TPP (**3**) synthesis using reagent concentrations at 0.3 M.

Entry	Flow rate (mL.min-1)	T (°C)	Residence time (min)	TPP (**3**) Yield (%)	STY (**3**) (g/day)
1	1.2	100	13	traces	-
2	1.2	120	13	6	4.5
3	1.2	140	13	5	4.3
4	1.2	160	13	3	2.2
5	0.6	100	27	traces	-
6	0.6	120	27	16	6.6
7	0.6	140	27	9	3.4
8	0.6	160	27	4	1.6
9	0.3	100	53	9	1.8
10	0.3	120	53	27	5.5
11	0.3	140	53	14	2.7
12	0.3	160	53	11	2.1

In general, the optimal temperatures are between 120°C and 140°C, since the other two studied temperatures lead to decreased yields. Regarding reagent concentration, 0.2M is the concentration of choice since the best yields of **3** were obtained under these conditions (13% at 1.2 mL.min^{-1}, 31% at 0.6 mL.min^{-1} and 29% at 0.3 mL.min^{-1}, Table 2). The optimal flow rates are 0.3 and 0.6 mL.min^{-1} in which the highest yields were obtained, but 0.6 mL.min^{-1} was ideal since it leads to a shorter residence time and consequently better STY.

In order to expand the utility of this work, we have performed gram scale synthesis of **3** under continuous flow conditions using 24 mmol of pyrrole (**1**) and 24 mmol of benzaldehyde (**2**) at 0.2 M, 120°C and 0.3 mL.min^{-1}. This experiment was planned to evaluate, at the same time, the best conditions to perform a gram-scale reaction (as in entry 10, Table 2), and also to test the long-term operating performance of the equipment without any blocking. This process worked easily and TPP (**3**) was isolated on a 1.1 g scale (29% yield). Under the same batch conditions, the Goncalves methodology[10] is described with no more than 10 mmol scale of reactants in 20% yield, thus demonstrating that our gram-scale results and the better space-time yield (8.2 g.day^{-1}) are very advantageous. We have also demonstrated two other important matters in flow chemistry, which are the reproducibility and the comparison with experiments in batch at the same residence time. During our studies we have checked the reproducibility of a number of experiments and obtained very good comparison. For example, in the case of entry 7, Table 1 we found 25% yield for the first experiment and 28% for the second, and for entry 10, Table 3, both yields were 27%. About the comparison between the batch and flow procedures, selected conditions from Tables 1-3 were evaluated. The equivalent batch condition for entry 7, Table 1, yielded porphyrin **3** in 14% against 25% under continuous flow; for entry 7, Table 2 yielded 25% against 31% under continuous flow, and for entry 10, Table 3 yielded 23% against 27% under continuous flow, all being lower in batch when compared to continuous flow conditions.



Scheme 2. *meso*-substituted porphyrin **5 a-f** synthesis under continuous flow conditions.

Table 4. Synthesis of *meso*-substituted porphyrins under continuous flow, 0.2 M reagent concentration, total flow rate of 0.6 mL.min-1 and residence time of 27 min.

Entry	Aldehydes	Porphyrin **5a-f** Yields (%)	STY (g/day)
1	4-methoxybenzaldehyde (**4a**)	25	7.9
2	3,5-di-*tert*-butylbenzaldehyde (**4b**) [(a)]	10	4.4
3	Methyl 4-formylbenzoate (**4c**)	13	4.7
4	2,3,4,5,6 – pentafluorobenzaldehyde (**4d**)	9	3.7
5	hexanal (**4e**) [(a),(b)]	19	4.8
6	decanal (**4f**) [(b)]	39	13.9

[(a)] the experiment was performed using 3 mmol of pyrrole (**1**) and 3 mmol of aldehyde (**4b**) due to limited availability of this compound. [(b)]The synthesis was performed at 150°C due to the lower reactivity of the aldehydes (4e-f)

In order to study the scope of *meso*-substituted porphyrin synthesis under continuous flow conditions, we have performed experiments with different aryl and alkyl aldehydes (Scheme 2, Table 4).

We have studied aromatic aldehydes substituted with electron donating groups (entries 1 and 2, Table 4) and electron withdrawing groups (entries 3 and 4, Table 4), and also aliphatic aldehydes (entry 5 and 6, Table 4). The reactions were performed using the optimized reaction conditions for

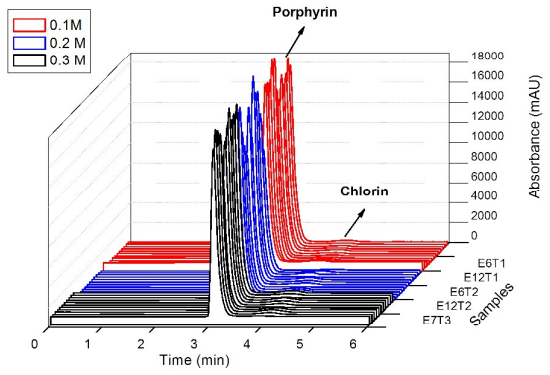


Figure 1. Chromatogram of all TPP (**3**) samples obtained in Table 1-3 (in red samples of Table 1, in blue of Table 2 and in black of Table 3). Elution in CH_2Cl_2 (1 mL.min^{-1}) using a diol silica gel column (250 mm x 4.6 mm I.D., 5 µm).

porphyrin **3** (0.2 M, flow rate of 0.6 mL.min^{-1} and temperature at 140°C). The yields for **5a-f** are 9 to 39% (Table 4) indicating that this optimized continuous flow protocol can also be used for the gram-scale synthesis of a variety of *meso*-substituted porphyrins.

In addition, it is known that porphyrins synthesised by the Rothemund[7], Adler,[8] or Goncalves[10] methodologies are almost always contaminated with the corresponding chlorin (non-oxidized intermediate). Therefore, in order to verify the purity of our isolated porphyrins, a relative quantification was carried out using HPLC-DAD-MS. We were able to determine the relative amounts of the porphyrins and their common impurities, comparing area bands from chromatograms (Figure 1).

HPLC-DAD-MS analysis confirmed the mass (m/z) of each product. All 36 samples of **3** (Table 1-3) and the other porphyrin derivatives (Table 4) were analysed using this hyphenated technique (Figure 1). Band areas for each compound between different runs were measured (among principal and secondary products), and the medium relative purity was around 98% for TPP (**3**) (ranging from 92 to 100% - Figure 1 and Table S1-S3, supporting information) and 2% for chlorin (ranging from 0 to 8%) (Figure 1 and Table S1-S3). All samples of **3** were eluted over a period of 3 min, whereas the correspondent chlorin exhibited an average retention time of 4 min (Table S1-S3, supporting information) when eluted with CH_2Cl_2 (1 mL.min^{-1}) and using a diol silica gel column (250 mm x 4.6 mm I.D., 5 µm). The ESI-MS analysis of these samples produced a molecular ion of m/z 615.2 $[M+H]^+$ for the first band, and m/z 617.4 [M+H]+ for the second band, which correspond to the porphyrin and the chlorin, respectively.

The UV-Vis Spectra (DAD detector) are also valuable tools for the characterization of porphyrins, due to the presence of four characteristic absorption bands at 514, 549, 589 and 645 nm, as well as for the characterization of chlorins, with bands at 518, 544, 598 and 652 nm.

The purities of all the porphyrins **5a-f** were also checked in similar chromatographic conditions (CH_2Cl_2 : Hexanes 9:1 at 1 mL.min^{-1} using a diol silica gel column (250 mm x 4.6 mm I.D., 5 µm). No chlorin derivatives were detected in all the porphyrins **5a-f** (Table S5 – supporting information), proving that this protocol is also very useful to produce highly pure *meso*-substituted porphyrins.

Experimental

General Methods

All reagents (analytical or HPLC grade) were purchased from Aldrich or national suppliers. When necessary, solvents and reagents were purified according to standard procedures.[26]

^{1}H and ^{13}C NMR spectra were recorded with a Bruker Avance 400 spectrometer at 400 and 101 MHz, respectively. $CDCl_3$ was used as solvent and TMS as the internal reference. The chemical shifts are expressed in δ (ppm) and coupling constants (*J*) are given in Hertz (Hz). The UV-Vis spectra were recorded with a Perkin–Elmer Lambda 25 spectrophotometer using 1 cm optical length quartz cuvettes at 25°C and dichloromethane as solvent.

All continuous flow experiments were carried out in an Asia Heater with an Asia 16 mL Stainless Steel Tube Reactor from Syrris (ID = 1.27 mm and OD = 1.6 mm), and an Asia Syringe Pump with blue syringes (500 µL and 1000 µL). LC-MS analyses of products were carried out in an Agilent 1200 series HPLC (Agilent, Santa Clara, USA) coupled to an API 2000 triple quadrupole (QqQ) Mass Spectrometer (Applied Biosystems, Concord, Canada), equipped with an electronspray ionization (ESI) source. The HPLC system, consisting of quaternary pump (G1311A), autosampler (G1367B), degasser (G1322A), thermostatted column compartment (G1316A), and diode-array detector (G1315D), was equipped with a diol silica gel column (250 mm x 4.6 mm I.D., 5 µm). The software used to control all HPLC and MS parameters was Analyst Software, version 1.5.1 (AB Sciex, CA, USA). This software was also used to acquire and process all chromatograms and spectral data. Analytical preparative thin-layer chromatography was performed on aluminium sheets (1 mm thick, Merck TLC silica-gel 60 F254.

Synthesis of *meso*-tetraphenylporphyrin (TPP) under continuous flow and optimization of reaction parameters: temperature, flow and concentration.

The TPP (**3**) syntheses were performed with pyrrole (**1**) and benzaldehyde (**2**) concentrations of 0.1, 0.2 and 0.3 mol.L^{-1}, reactor temperatures of 100°C, 120°C, 140°C and 160°C, and total flow rates of 0.3, 0.6 and 1.2 mL.min^{-1}. Thus, propionic acid (25.3, 38.6 or 78.6 mL) (pump 1) and 12 mmol of pyrrole (**1**) (0.83 mL), 12 mmol of benzaldehyde (1.22 mL) and nitrobenzene (12.6, 19.3 or 39.3 mL) (pump 2) were

simultaneously pumped following the flow rate of 2:1, respectively. All products were isolated by precipitation from methanol and crystallization from CH_2Cl_2 (a few drops) and methanol. TPP (**3**) was obtained as a purple crystalline solid ranging from traces to 31% yield. **^{1}H NMR** (400 MHz, $CDCl_3$) δ (ppm): -2.78 (s, 2H, N-H); 7.67 - 7.83 (m, 12H, Ph-H^{m,p}); 8.22 (dd.*J* = 7.6, 1.7 Hz, 8H, Ph-H^o); 8.84 (s, 8H β-H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ (ppm): 120.1, 126.7, 127.7, 131.3, 134.6, 142.2. **UV-Vis** (CH_2Cl_2): λmax (logε) 417 (5.69); 514 (4.26); 549 (3.88); 589 (3.72); 645 (3.61) nm.

Extension of reaction scope under continuous flow

Propionic acid (38.6 mL) was pumped (pump 1) with a flow rate of 0.386 mL.min^{-1} and pyrrole (12 mmol), the aldehyde (12 mmol) and nitrobenzene (19.3 mL) pumped (pump 2) with a flow rate of 0.214 mL.min^{-1} (total flow rate 0.600 mL.min^{-1} and residence time 27 min). The reactor temperature was kept at 140°C. The products were isolated by crystallization from methanol.

***meso*-tetra(4-methoxyphenyl)porphyrin:** 25% yield (0.75 mmol, 0.551 g). **^{1}H NMR** (400 MHz, $CDCl_3$) δ (ppm): -2.75 (s, 2H, N-H); 4.10 (s, 12H, Ph-OMe-H); 7.29 (d, *J* = 8.6 Hz, 8H, Ph-H^m); 8.12 (d, *J* = 8.6 Hz, 8H, Ph-H^o); 8.86 (s, 8H, β-H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ (ppm): 112.3, 122.8, 123.1, 123.43, 134.8, 135.7. **UV-Vis** (CH_2Cl_2): λmax (logε) 421 (5.61); 518 (4.24); 555 (4.06); 593 (3.71); 650 (3.78) nm.

***meso*-tetra(3,5-di-tert-butylphenyl)porphyrin:** prepared by the optimized procedure for TPP synthesis, but using 3 mmol of pyrrole (**1**) and 3 mmol of 3,5-di-*tert*-butylbenzaldehyde, thus giving the porphyrin **5b** in 10 % yield (0.07 mmol, 0.076 g). **^{1}H NMR** (400 MHz, $CDCl_3$) δ (ppm): -2.67 (s, 2H, N-H); 1.52 (s, 72H, Ph-tBu-H); 7.78 (t, *J* = 1.8 Hz, 4H, Ph-H^p); 8.09 (d, *J* = 1.8 Hz, 8H, Ph-H^o); 8.89 (s, 8H, β-H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ (ppm): 29.9, 31.9, 35.2, 121.1, 121.4, 129.8, 141.5, 148.8. **UV-Vis** (CH_2Cl_2): λmax (logε) 420 (5.86); 517 (4.26); 553 (4.01); 592 (3.72); 647 (3.75) nm.

***meso*-tetra(4-methoxycarbonylphenyl)porphyrin:** 13% yield (0.38 mmol, 0.325 g). **^{1}H NMR** (400 MHz, $CDCl_3$) δ (ppm): -2.80 (s, 2H, N-H); 4.11 (s, 12H, Ph-CO_2Me-H); 8.29 (d, *J* = 8.3 Hz, 8H, Ph-H^m); 8.45 (d, *J* = 8.3 Hz, 8H, Ph-H^o); 8.82 (s, 8H, β-H). **^{13}C NMR** (101 MHz, CDCl3) δ (ppm): 29.9, 52.6, 119.6, 128.1, 129.9, 134.7, 146.8, 167.4. **UV-Vis** (CH_2Cl_2): λmax (logε) 419 (5.67); 515 (4.26); 549 (3.97); 589 (3.82); 645 (3.63) nm.

***meso*-tetra(pentafluorophenyl)porphyrin:** Porphyrin **5d** was isolated by evaporation of solvents and purified over silica gel using hexanes as eluent. 9% yield (0.26 mmol, 0.256 g). **^{1}H NMR** (400 MHz, $CDCl_3$) δ (ppm): -2.91 (s, 2H, N-H); 8.92 (s, 8H, β-H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ (ppm): 103.8, 115.7, 131.4, 136.5, 139.0, 141.2, 143.8, 145.4, 147.9 **UV-Vis** (CH_2Cl_2): λmax (logε) 411 (5.39); 506 (4.24); 535 (3.36); 582 (3.76); 636 (2.94) nm.

***meso*-tetra(pentyl)porphyrin: 5e** was prepared by the optimized procedure for TPP synthesis, but using 3 mmol of pyrrole (**1**) and 3 mmol of hexanal at 150°C and the porphyrin was obtained in 19% yield (0.14 mmol, 0.084 g). **^{1}H NMR** (400 MHz, $CDCl_3$) δ (ppm): -2.64 (s, 2H, N-H); 0.99 (t, *J* = 7.3 Hz, 12H, CH_3-H^5); 1.45-1.65 (m, 18H, CH_2-H^4, H2O); 1.65-1.99 (m, 8H, CH_2-H^3); 2.35-2.69 (m, 8H, CH_2-H^2), 4.79-5.06 (m, 8H, CH_2-H^1); 9.46 (s, 8H, β-H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ (ppm): 13.1, 21.7, 28.7, 31.7, 34.4, 37.3, 117.3, 127.0. **UV-Vis** (CH_2Cl_2): λmax (logε) 417 (5.61); 520 (3.95); 555 (3.77); 600 (3.39); 659 (3.63) nm.

***meso*-tetra(nonyl)porphyrin: 5f** was prepared by the optimized procedure for TPP synthesis, but it was performed at 150°C, thus giving the corresponding porphyrin in 39% yield (0.30 mmol, 0.241 g). **^{1}H NMR** (400 MHz, $CDCl_3$) δ (ppm): -2.74 (s, 2H, N-H); 0.81 (t, *J* = 6.6 Hz, 12H, CH_3-H^9); 1.19 - 1.36 (m, 32H, CH_2-H^{5,6,7,8}); 1.44 (dt, *J* = 14.7, 7.3 Hz, 8H, CH_2-H^4); 1.71 (dt, *J* = 15.0, 7.6 Hz, 8H, CH_2-H^3); 2.42 (dt, *J* = 14.6, 7.6 Hz, 8H, CH_2-H^2); 4.82 (t, *J* = 7.9 Hz, 8H, CH_3-H^1); 9.35 (s, 8H, β-H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ (ppm): 14.3, 22.8, 29.6, 29.86, 29.9, 30.8, 32.1, 35.7, 38.9, 51.0, 53.6, 118.5. **UV-Vis** (CH_2Cl_2): λmax (logε) 417 (5.15); 520 (3.79); 555 (3.67); 600 (3.42); 658 (3.46) nm.

Determination of porphyrin purity by LC/MS analysis

In all separation analyses, the mobile phase was an isocratic mode using dichloromethane and hexane (HPLC grade) at 90:10 v/v for compounds **5a-f** and only dichloromethane for **3**. The column temperature was maintained at 21^{o}C, the flow rate 1.0 mL.min^{-1}, the injection volume 10 µL, and the detection wavelength was set at 400 - 800 nm. Mass analyses were carried out in full scan mode from 200 to 1000 a.m.u., in the positive ion mode. The ionization of the samples was carried out with electronspray ionization (ESI). All assays using HPLC were performed allowing the introduction of only 50 uL.min^{-1} of column eluent into the MS source, in order to achieve an adequate flow rate for ESI-MS analysis. MS parameters were first optimized by direct infusion of a standard solution (5 µg.mL^{-1}) at 20 µL.min^{-1} flow. The universal parameters used in all mass spectra were as follows: source dependent parameters as nebulising gas (GS1), curtain gas and heater gas were (GS2) set as 30, 30 and 10 a.u. (arbitrary units), respectively. The temperature of the ion source was set at 300^{o}C, and ion spray voltage +5000 V. The analyte dependent parameters focusing potential (FP), entrance potential (EP) and decluttering potential (DP) were set as -28, -10 and -14 V, respectively. Data and spectra of all compounds can be found in the supporting information.

Conclusions

In conclusion, we have demonstrated an efficient continuous flow protocol for *meso*-substituted porphyrin synthesis in a safe, reproducible, gram-scale and temperature controlled manner. Good yields were obtained considering the general literature for these compounds, whose preparation involves four aromatic substitutions, one cyclisation and the oxidation of four hydrogens (multi-step one-pot reaction). Most important, all the products were easily isolated with high purity, since the use of flow chemistry appears to diminish the formation of polymeric by-products.

Acknowledgements

The authors would like to thank the São Paulo Research Foundation (FAPESP) (2013/06532-4, 2013/07276-1 and 2011/13993-2), CNPq and CAPES for financial support. P.B. Momo thanks CNPq for a fellowship. Thanks are also due to Prof. Dr. Antonio G. Ferreira and Luciana Vizotto for the NMR analyses, and Prof. Dr. Moacir Rossi Forim for the HPLC-DAD-MS facilities.

Notes and References

‡Electronic Supplementary Information (ESI) available: copy of UV-Vis, ^{1}H and ^{13}C NMR spectra, LC/MS data and spectra of all compounds. See DOI: 10.1039/x0xx00000x

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